

## REMARKS

Claims 1-36 are pending in the present application. Claims 5-8 are rejected.

Claims 1-4 and 9-36 are withdrawn from consideration as being drawn to a non-elected invention. Upon entry of the instant Amendment, claims 5 and 6 will be pending. Claim 5 is amended to recite the particular SEQ ID NOs. exemplified in the specification, and claim 6 is amended as requested by the Examiner to clarify the fusion protein.

### *Objection to the Claims*

The Examiner still objects to claims 6 and 8 as not being narrower than the claims they depend from. Applicants herein rewrite claim 6 as requested by the Examiner. Claim 8 is canceled without prejudice.

### *Rejection under 35 USC 112, first paragraph*

The Examiner maintains the rejection of claims 5-8 as not properly enabled based upon the rationale that the specification fails to teach “how to use” this broad genus of peptides. The Examiner’s reasoning is that there is a large genus, there is no identification of a ligand for most of the peptide species, and there is no identification of a specific biological function for most of the peptide species. Further, the Examiner says that one of ordinary skill in the art would not know which bromodomain peptides would bind to which acetyl lysine containing peptides. The Examiner dismisses the supplemental evidence Applicants provided regarding the bromodomains of other proteins.

The Examiner notes that these claims read on peptides comprising the ZA loop of protein bromodomains that fall within an indicated generic structure, that of SEQ ID NO: 3. Purely in the interest of advancing prosecution, Applicants refer to the particular SEQ ID NOs presented in claim 7 and exemplified in the specification in place of the more generic SEQ ID NO: 3. However, Applicants expressly reserve the right to pursue the subject matter of the more generic SEQ ID NO: 3 and all of the other SEQ ID NOs.

representing additional ZA loops of additional bromodomains in other patent applications.

Applicants previously submitted that because teachings regarding the potential use of the P/CAF bromodomain are explicitly set forth, those skilled in the art would be able to use any ZA loop of any bromodomain.

Applicants respectfully submit that the patent law does not require any particular number of species to describe a genus. Nonetheless, Applicants previously submitted the Declaration of Dr. Ming-Ming Zhou pursuant to 37 C.F.R. 1.132 wherein the Declarant clarified that he is aware of many proteins containing a bromodomain that have been shown to interact with other proteins. Representative examples include the bromodomain of WSTF (Williams syndrome transcription factor) that interacts with lysine-acetylated histones (Fujiki, R., et al., *Ligand-induced transrepression by VDR through association of WSTF with acetylated histones*. Embo J, 2005); the bromodomain of the transcriptional cofactor p300 that binds to nucleosome (Ragvin, A., et al., *Nucleosome binding by the bromodomain and PHD finger of the transcriptional cofactor p300*. J Mol Biol, 2004. 337(4): p. 773-88); the bromodomain of CBP/p300 that binds to acetylated MyoD (Polesskaya, A., et al., *Interaction between acetylated MyoD and the bromodomain of CBP and/or p300*. Mol Cell Biol, 2001. 21(16): p. 5312-20); the bromodomain of NoRC (the SNF2h-containing chromatin-remodeling complex) that interacts with K16-acetylated histone H4 (Zhou, Y. and I. Grummt, *The PHD finger/bromodomain of NoRC interacts with acetylated histone H4K16 and is sufficient for rDNA silencing*. Curr Biol, 2005. 15(15): p. 1434-8); the bromodomains of BDF1 and BDF2 that bind to histone H4 (Matangkasombut, O., et al., *Bromodomain factor 1 corresponds to a missing piece of yeast TFIID*. Genes Dev, 2000. 14(8): p. 951-62); the bromodomain of the WBSCR9 gene, encoding a novel transcriptional regulator, in the Williams-Beuren syndrome deletion at 7q11.23 (Peoples, R.J., et al., *Identification of the WBSCR9 gene, encoding a novel transcriptional regulator, in the Williams-Beuren syndrome deletion at 7q11.23*. Cytogenet Cell Genet, 1998. 82(3-4): p. 238-46); the bromodomain-containing TIF1 $\alpha$ : a possible link between KRAB zinc finger proteins and nuclear receptors (Le Douarin, B., et al., *TIF1alpha: a possible link between KRAB zinc finger proteins and nuclear receptors*. J Steroid Biochem Mol Biol, 1998. 65(1-6): p. 43-50); and, the bromodomain

of CBP that interacts with human tumor suppressor p53 at acetylated lysine 372 (Mujtaba, S., et al., *Structural mechanism of the bromodomain of the coactivator CBP in p53 transcriptional activation*. Mol Cell, 2004. **13**(2): p. 251-63). (See, Paragraph 5) In view of this wealth of information in the art, it is clear that one of skill in the art has a wealth of bromodomains at his or her disposal. As such, a skilled artisan may practice the invention without undue experimentation.

Dr. Ming-Ming Zhou, in the Declaration previously submitted pursuant to 37 C.F.R. 1.132, clarified that he is aware of many proteins containing a bromodomain that have been shown to interact with other proteins and for which the consequence of this interaction is understood as regards biological activity. Examples of these include that the bromodomain containing 2 (Brd2) is expressed in distinct patterns during ovarian folliculogenesis independent of FSH or GDF9 action (Trousdale, R.K. and D.J. Wolgemuth, *Bromodomain containing 2 (Brd2) is expressed in distinct patterns during ovarian folliculogenesis independent of FSH or GDF9 action*. Mol Reprod Dev, 2004. **68**(3): p. 261-8); the bromodomain of the MLL-CBP fusion protein is required for generating a myelodysplastic-like syndrome that evolves into myeloid leukemia (Lavau, C., et al., *Chromatin-related properties of CBP fused to MLL generate a myelodysplastic-like syndrome that evolves into myeloid leukemia*. EMBO J., 2000. **19**: p. 4655-4664); the bromodomain-containing histone H3 acetylase dGcn5 is a key player in Drosophila melanogaster metamorphosis(Carre, C., et al., *The histone H3 acetylase dGcn5 is a key player in Drosophila melanogaster metamorphosis*. Mol Cell Biol, 2005. **25**(18): p. 8228-38); the bromodomain protein Brd4 is a positive regulatory component of P-TEFb and stimulates RNA polymerase II-dependent transcription (Jang, M.K., et al., *The bromodomain protein Brd4 is a positive regulatory component of P-TEFb and stimulates RNA polymerase II-dependent transcription*. Mol Cell, 2005. **19**(4): p. 523-34); the PHD finger/bromodomain of NoRC interacts with acetylated histone H4K16 and is sufficient for rDNA silencing (Jang, M.K., et al., *The bromodomain protein Brd4 is a positive regulatory component of P-TEFb and stimulates RNA polymerase II-dependent transcription*. Mol Cell, 2005. **19**(4): p. 523-34); the bromodomain-containing protein Bdflp acts as a phenotypic and transcriptional multicopy suppressor of YAF9 deletion in yeast (Bianchi, M.M., et al., *The bromodomain-containing protein Bdflp acts as a*

*phenotypic and transcriptional multicopy suppressor of YAF9 deletion in yeast.* Mol Microbiol, 2004. **53**(3): p. 953-68); Bdf1 bromodomains' interactions with acetylated H4 tails help anchor the transcriptional protein complex TFIID to the promoter during the initial stages of transcription activation (Martinez-Campa, C., et al., *Precise nucleosome positioning and the TATA box dictate requirements for the histone H4 tail and the bromodomain factor Bdf1*. Mol Cell, 2004. **15**(1): p. 69-81); the CBP bromodomain and nucleosome targets are required for Zta-directed nucleosome acetylation and transcription activation (Deng, Z., et al., *The CBP bromodomain and nucleosome targeting are required for Zta-directed nucleosome acetylation and transcription activation*. Mol Cell Biol, 2003. **23**(8): p. 2633-44); the bromodomains anchor chromatin-modifying complexes to promoter nucleosomes (Hassan, A.H., et al., *Function and selectivity of bromodomains in anchoring chromatin-modifying complexes to promoter nucleosomes*. Cell, 2002. **111**: p. 369-379); the bromodomain mediates transcriptional intermediary factor 1alpha -nucleosome interactions (Remboutsika, E., et al., *The bromodomain mediates transcriptional intermediary factor 1alpha -nucleosome interactions*. J Biol Chem, 2002. **277**(52): p. 50318-25). (See, paragraph 7)

Dr. Ming-Ming Zhou, in the Declaration pursuant to 37 C.F.R. 1.132, clarified that he is aware of many proteins that have been shown to interact with the bromodomain of another protein. Representative examples include nucleosomal core histones H3, H4, H2A and H2B, each of which has multiple known lysine acetylation sites. In addition, other proteins including cellular proteins of p53 (Mujtaba, S., et al., *Structural mechanism of the bromodomain of the coactivator CBP in p53 transcriptional activation*. Mol Cell, 2004. **13**(2): p. 251-63); NF- $\kappa$ B (Greene, W.C. and L.F. Chen, *Regulation of NF- $\kappa$ B action by reversible acetylation*. Novartis Found Symp, 2004. **259**: p. 208-17; discussion 218-25) and HIF1 $\alpha$  (Chun, Y.S., et al., *Phorbol ester stimulates the nonhypoxic induction of a novel hypoxia-inducible factor 1alpha isoform: implications for tumor promotion*. Cancer Res, 2003. **63**(24): p. 8700-7) interact with a bromodomain of another protein. (See, paragraph 6) In view of this wealth of information in the art, it is clear that one of skill in the art has a wealth of bromodomains and their corresponding ligand at his or her disposal. As such, a skilled artisan may practice the invention without undue experimentation.

As regards the acetyl-lysine that is bound, Applicants again refer to the Declaration of Dr. Ming-Ming Zhou pursuant to 37 C.F.R. 1.132 wherein the Declarant clarified that as reported in the specification, some bromodomains may not bind to the free amino acid acetyl-lysine alone. This may be due to the charged amino and/or carboxyl groups of the amino acid lysine that are adjacent to its acetyl moiety. However, bromodomains do in fact interact with and bind to an acetyl-lysine residue when it is presented in a polypeptide sequence such as those in proteins. In latter cases, these charged groups may be naturalized due to polypeptide connectivity. Hence, the acetyl lysine may be necessary for bromodomains to bind to a particular portion of a protein. (See, paragraph 8)

***Rejection under 35 USC 102***

The Examiner maintains the rejection of claims 6 and 8 in part as anticipated by Denis and Green, Genes Dev 10(3):261-271. The Examiner recommends changing the claims to recite “A fusion protein consisting of a first sequence consisting of a ZA loop of a bromodomain according to SEQ ID NO: 19, and a second sequence from another protein.” Applicants herein make the requested change.

***Fees***

No fees are believed to be necessary in connection with this response. However, if this is in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or credit any overages.

*Conclusion*

Applicants believe that the foregoing amendments to the claims place the application in condition for allowance. Withdrawal of the rejections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 114, to effect a resolution.

Respectfully submitted,

  
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